Remarks

Rejections under 35 U.S.C. §112

Claims 1-3 and 27-48 stand rejected as failing to comply with the written description requirement. The Examiner bases this rejection on the Federal Circuit's alleged holding in *Regents of the University of California v. Eli Lilly* that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus (Office Action of 10/27/05, pp. 3-4) and further on the alleged holding of *Fiers v. Revel* that adequate written description of a protein requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it (Office Action , p. 5). Applicants respectfully submit that these cases do not provide grounds to reject the instant claims and respectfully request reconsideration and withdrawal of the rejection for each of the following reasons.

Firstly, Applicant is not describing a genus of nucleic acids based solely on its function as suggested by the Examiner. Instead, the claimed genus of nucleic acids must encode a protein that meets the structural requirements that allow the protein to interact with and hydrolyze a substrate that is specifically hydrolyzed by lysostaphin, i.e., the pentapeptide links of *S. aureus* cell walls. Such structural requirements are akin to those that distinguish one antibody from another. As pointed out in the Office Action Response filed August 31, 2005, the Federal Circuit and the USPTO Written Description Guidelines have recognized that similar structural requirements, namely those that define an antibody based on its ability to bind to a particlar antigen, are sufficient to describe the antibody even in the absence of a specific embodiment of the antibody (see, e.g., Example 16 of the Written Description Guidelines and *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed.Cir.1986)). Although antibodies do share overall structural features, the distiction between different antibodies, which must be described in order to meet the written description requirements, lies in the antigen-binding region. The Examiner has dismissed this argument on the ground that "this is simply not applicable to claims directed to nucleic acids". Applicants respectfully submit that the Examiner is incorrect. The nucleic acids claimed here are defined by the fact that they encode an active lysostaphin protein. Variations in the nucleic acid sequence arise as a result of the genetic code, according to which certain amino acids can be encoded by more than one different codon. Given

a protein sequence, it is well within the skill of one in the art to generate every possible nucleic acid that could encode it. Since the claimed nucleic acids are defined by virtue of the protein that they encode, the example of written description of an antibody, which is simply a protein, is directly applicable to the instant claims.

Secondly, and related to the above argument, Applicants point out that unlike the situation in *Lilly*, the claims are not directed to specific, *naturally occurring* nucleic acids such as the "vertebrate insulin cDNA" of *Lilly*. At most, the Federal Circuit's holding in *Lilly* indicated that in order to claim a specific, naturally occurring nucleic acid one must describe its actual sequence, e.g., so as to distinguish that nucleic acid from other nucleic acids that might encode the same protein. Here, Applicants are *not* specifically claiming naturally occurring nucleic acid sequences that encode active lysostaphin. Thus it is the holding in *Lilly* that is "simply not applicable" to the instant claims rather than the USPTO Written Description Guidelines' teachings with respect to antibody-antigen interactions.

Thirdly, as the undersigned explained briefly on the phone, a conclusion that the instant claims meet the written description requirement flows directly from the recently decided case of *Invitrogen Corporation v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 77 U.S.P.Q.2d 1161, (Fed. Cir. 2005). In that case the Federal Circuit affirmed that claims in U.S. Pat. No. 6,063,608 (the '608 patent), whose relevant elements are substantially similar in language to the instant claims in many respects, met the written description requirement. Rejecting a challenge based on the holdings of *Lilly* and *Fiers*, the court held that claim 1 of the '608 patent, which recites, "An isolated polypeptide having DNA polymerase activity and substantially reduced RNase H activity, wherein said polypeptide is encoded by a *modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence* resulting in said polypeptide having substantially reduced RNase H activity, and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, Neurospora, Drosophila, primates and rodents." (emphasis added) is adequately described. See, *Invitrogen*, 429 F.3d 1052 at 1071-1075, 77 U.S.P.Q.2d 1161 at 1174-1176 (Fed. Cir. 2005).

The Examiner's attention is drawn to the similarity between this claim and the instant claim 1. The "isolated polypeptide" of claim 1 of the '608 patent is encoded by "a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence..." while the instant claim 1 recites, "An isolated nucleic acid comprising a modified gene, the gene

including a sequence that codes for a lysostaphin protein, wherein the lysostaphin protein differs from a naturally occurring version of lysostaphin...". The '608 patent describes that "RT genes having DNA polymerase activity and substantially no RNase H activity may be obtained by deletion of deoxyribonucleotides at the 3' end of the gene which encode the portion of the polypeptide having RNase H activity (col. 10, lines 57-62). However, the patent does not limit the claimed genus to polypeptides obtained by making only this modification to a naturally occurring RT and does not describe how much of the 3' end of the gene may be deleted while retaining DNA polymerase activity and does not describe which features of RT must be retained in order to preserve the recited functions. Claim 1 of the '608 patent recites that the nucleotide sequence is "derived from" any of a variety of organisms. While the '608 patent refers to nucleotide sequences encoding reverse transcriptase (RT) that are found in some of the listed organisms, it does not define "derived from". Neither does the list of organisms limit the scope of the sequences as the claim is not restricted to *known* sequences but could encompass any sequence encoding a polypeptide with reverse transcriptase activity, including those yet to be discovered. Applicants submit that any nucleotide sequence ranging from a single nucleotide to the human genome could be "derived from" any other nucleotide sequence by making a sufficient number of additions, substitutions, and/or deletions if one were to follow the Examiner's reasoning according to which an altered lysostaphin protein could encompass structural variants in which every single amino acid is altered except for one site (see Office Action, p. 5). Thus the mere existence of multiple RT genes does not distinguish claim 1 of the '608 patent from claim 1 of the instant application in terms of fulfilling the written description requirement.

The only way that one of skill in the art could determine whether any particular modified RT "derived from" the RT of a particular organism meets the functional requirements of the claims of the '608 patent is by testing the modified RT for the recited activities. The '608 patent acknowledges that the skilled artisan would need to test the modified RT derived from a naturally occurring RT in order to determine whether it indeed possessed DNA polymerase activity (see col. 11, lines 5-9, referring to methods that one of skill in the art could use to test whether the modified RT possessed DNA polymerase activity). The Federal Circuit recognized that the '608 patent, "claims a compound (the polypeptide or genetically engineered RT) in terms

of biological functions (DNA polymerase and RNase H activity)". *Invitrogen*, 429 F.3d 1052 at 1072-1073; 77 U.S.P.Q.2d 1161 at 1174.

As noted above, Clontech's assertion that the claims in the '608 patent (and a second related patent) failed to meet the written description requirement was based on the holdings of *Lilly* and *Fiers*. The Federal Circuit held that, "Clontech's appeal to *Eli Lilly* and *Fiers* is misplaced. In those cases the patent specifications at issue did not identify the sequence (structure) of any embodiment of DNA claimed therein...In contrast, the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features – DNA polymerase activity without RNase H activity. Under both *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient." *Invitrogen*, 429 F.3d 1052 at 1073, 77 U.S.P.Q.2d 1161 at 1175. Note that this holding does not rely on the fact that multiple RT species were known when the '608 patent was filed but is simply based on the fact that the '608 patent discloses DNA and amino acid sequences of a single representative species of the clamed genus and methods for determining that the enzyme possesses the claimed features.

The '608 patent almost precisely parallels the instant patent application. The instant specification describes naturally occurring active lysostaphin and describes that the lysostaphin protein and nucleotide sequence encoding it may be modified to produce active lysostaphin that is secreted by mammalian cells in its active form and kills *Staphylococcus aureus* cells by hydrolyzing pentapeptide links of *Staphylococcus aureus* cell walls by altering one or both sites for glycosylation in mammalian cells. The specification further describes methods that could be used to determine whether any particular modified lysostaphin protein possesses the functional features recited in the claims. It is clear that the claimed nucleotide sequences encode an altered lysostaphin that is "derived from" naturally occurring lysostaphin within the meaning of the word "derived" in the '608 patent and will therefore differ from the naturally occurring sequence in a manner consistent with preservation of activity, just as in the case of the modified RT of the '608 patent. See, e.g., paragraph 61 of the instant specification (p. 16, lines 1-16), stating that, "various changes to the precise lysostaphin amino acid sequence can readily be made without interfering with...lysostaphin activity... Those of ordinary skill in the art ... may employ any known technique, including those described herein, to assay the proteins produced from genes

containing such modifications in order to determine whether such genes encode functional proteins as required by the present inventiongenes that direct expression and secretion of an active lysostaphin protein with one or more sequence differences from naturally-occurring lysostaphin (SEQ ID NO:1) or from the particular altered lysostaphin described herein (SEQ ID NO:3) are considered to be "functional equivalents" of the altered lysostaphin described herein, and are within the scope of the present invention."

In summary, the '608 patent claims a modified polypeptide based solely on its functional characteristics and a single representative embodiment. The Federal Circuit held that the '608 specification was sufficient because, unlike the patents at issue in *Lilly* and *Fiers* the '608 patent described a representative embodiment of the claimed polypeptide by nucleotide and amino acid sequence and provided methods by which one of ordinary skill in the art could determine whether any particular modified RT possessed the claimed features. The instant patent application describes at least one representative embodiment of an altered lysostaphin protein possessing the claimed features by nucleotide and amino acid sequence and provides methods by which one of ordinary skill in the art could determine whether any particular modified lysostaphin possesses the claimed features. Therefore, Applicants submit that the holding in *Invitrogen*, which clarifies the lack of relevance of *Lilly* and *Fiers* to claims to nucleic acids or proteins that are based at least in part on function *and are supported by a representative embodiment*, mandates a conclusion that the instant claims meet the written description requirement. Accordingly, withdrawal of the rejection is respectfully requested.

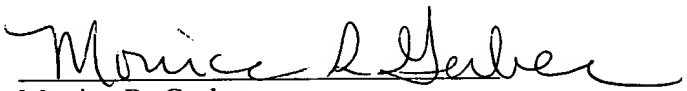
Applicants have amended claim 45 in a manner that is believed to limit the claimed nucleic acids to those species that encode the protein of SEQ ID NO: 3 or that encode variants that differ from SEQ ID NO: 3 only in that one or both of their sites for mammalian glycosylation Asn-X-(Ser/Thr) is altered, which was the intent of the original language, and have added claim 49, drawn to certain of these species. However, as described *supra*, the claimed invention is no way limited to these species. Withdrawal of the rejection of claim 45 and claims dependent therefrom is respectfully requested.

In conclusion, in view of the amendments and remarks presented herein, the application complies with the requirements of 35 U.S.C. §112. Applicants therefore respectfully submit that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5000 or (617) 248-5071 (direct dial).

A petition for a one (1) month extension of time and American Express credit card form to cover the fee for an extension of time are enclosed. Please charge any additional fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,



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